



Comparative efficacy of once-daily ciclesonide and budesonide in the treatment of persistent asthma

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Summary

Background: The aim of this study was to compare the efficacy and safety of once-daily ciclesonide, a new-generation, on-site-activated, inhaled corticosteroid, with once-daily budesonide in persistent asthma.

Methods: Eligible patients requiring budesonide or equivalent 320–640 µg (ex-mouthpiece, equivalent to 400–800 µg; TurbohalerTM) daily entered a 2-week baseline, and then a 2- to 4-week pretreatment period (budesonide 1280 µg/day; ex-mouthpiece, equivalent to 1600 µg/day). Patients with an increase in forced expiratory volume in 1 s (FEV₁) of $\geq 7\%$ or ≥ 0.15 L were randomised to ciclesonide 320 µg (ex-actuator, equivalent to 400 µg ex-valve) via a hydrofluoroalkane-metered dose inhaler (HFA-MDI) without a spacer or budesonide 320 µg once daily in the morning for 12 weeks. Change in FEV₁ was the primary endpoint.

Results: In all, 359 patients were randomised. The FEV₁ and forced vital capacity (FVC) decreased by 0.18 and 0.12 L, respectively, in the ciclesonide group, and by 0.23 and 0.21 L in the budesonide group. For FEV₁, ciclesonide was noninferior and numerically superior to budesonide. For FVC, ciclesonide was statistically superior to budesonide ($P = 0.010$). Asthma symptom scores were comparable; the median percentage of symptom-free days was significantly higher for ciclesonide (43.6%) versus budesonide (25.8%) ($P = 0.017$). Rescue medication use decreased significantly only for ciclesonide patients ($P = 0.009$). Frequency of adverse events was low in both groups.

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Conclusion: Ciclesonide 320 µg once daily by HFA-MDI without a spacer was at least as effective as budesonide 320 µg once daily in persistent asthma.
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Introduction

Inhaled corticosteroids (ICS) are recommended as first-line therapy for patients with persistent asthma.¹ However, some physicians as well as patients are still concerned about the potential local and systemic side effects associated with these medications.² Even though the currently available ICS are effective and safe at the recommended doses, development of a novel agent with potent anti-inflammatory activity and an improved safety profile is a welcome addition.³

Ciclesonide is an ICS administered as an inactive parent compound that is converted to its active metabolite, desisobutyl-ciclesonide (des-CIC), by esterase-mediated hydrolysis in the lung.^{4,5} The active metabolite, des-CIC, has a 100-fold greater relative glucocorticoid receptor binding affinity than ciclesonide (relative glucocorticoid receptor binding affinities are 1200 and 12, respectively; dexamethasone reference is 100). In addition, des-CIC undergoes extensive lipid conjugation that creates an active drug reservoir ensuring prolonged pulmonary residence time and continuous 24-h anti-inflammatory activity ideal for once-daily treatment regimens.^{6,7} Furthermore, des-CIC is highly protein bound and rapidly metabolised, leaving <1% of free drug in the systemic circulation and potentially reducing systemic adverse effects.^{7,8}

The clinical efficacy and safety of ciclesonide have been demonstrated in several studies. Ciclesonide has been shown to be effective at dose ranges from 80 to 640 µg (ex-actuator, equivalent to 100–800 µg ex-valve) once daily in maintaining lung function in patients with mild-to-moderate persistent asthma compared with placebo following pretreatment with 400–1000 µg/day beclomethasone or equivalent.^{9,10} Ciclesonide has also been shown to effectively reduce airway hyperresponsiveness to adenosine-5'-monophosphate-induced bronchoconstriction as well as early- and late-phase allergen-induced asthmatic reactions.^{11,12} Moreover, ciclesonide 160 µg (ex-actuator, equivalent to 200 µg ex-valve) administered once daily in the morning or evening was shown to significantly improve pulmonary function and control of asthma symptoms.¹³

Ciclesonide is at least as effective as budesonide, but has shown a superior safety profile in earlier

preclinical, anti-inflammatory studies.¹⁴ However, there is no direct comparison of clinical profiles of ciclesonide and budesonide using the same dose and schedule. Therefore, the primary objective of this study was to compare the efficacy and safety of ciclesonide 320 µg (ex-actuator, equivalent to 400 µg ex-valve) with budesonide 320 µg (ex-mouthpiece, equivalent to 400 µg; Turbohaler™) once daily over 12 weeks.

Methods

Patients

Eligible patients were between 12 and 75 years of age with a diagnosis of persistent asthma for at least 6 months as defined by the American Thoracic Society criteria.¹⁵ Inclusion criteria to enter the baseline period included a forced expiratory volume in 1 s (FEV₁) of 65–95% of predicted value depending on pretreatment—the dose of ICS (budesonide 320–640 µg or equivalent) and the addition of other controller medications (long-acting β_2 -agonists, leukotriene antagonists, or equivalent).

Exclusion criteria included concomitant severe diseases or contraindications for the use of ICS; clinically relevant abnormal laboratory values suggesting unknown disease; an asthma exacerbation or infection of the lower airways within 4 weeks before entering the baseline period; and emergency treatment or hospital admission for asthma within 4 weeks before the baseline period. Additional exclusion criteria included use of systemic steroids within 4 weeks or injectable depot steroids within 6 weeks before entering the baseline period or more than three times during the last 6 months; evidence of chronic obstructive pulmonary disease or other relevant lung diseases; heavy smokers or ex-smokers (>10 cigarettes/day or >2 pipes/day); suspected noncompliance; drug abuse; or pregnancy.

Study design

This was a multicentre, randomised, double-blind, double-dummy, parallel-group study. The Ethics Committee of each participating site approved

the study, and all patients provided written, informed consent. The study included three distinct periods: a 2-week baseline period, a 2- or 4-week pretreatment period (duration depending on the response to budesonide administered during the first 2 weeks), and a 12-week treatment period. Patients had been maintained on a constant dose of ICS that included budesonide 320–640 µg/day (ex-mouthpiece or the actual dose delivered to the patient from the Turbohaler mouthpiece, equivalent to 400–800 µg; Turbohaler™), fluticasone propionate 176–440 µg/day (ex-actuator or the actual dose delivered to the patient from the outlet of the metered-dose inhaler (MDI), equivalent to 200–500 µg ex-valve, the amount of drug released by the valve of inhaler into the mouthpiece), or equivalent for 4 weeks before baseline.

During the baseline period, all patients continued their usual dosage of ICS and rescue medication as needed, but all other anti-asthma controller medications were not permitted. Subsequently, patients entered the pretreatment period if they had an asthma symptom score sum of at least four or a total of eight or more doses of rescue medication within 4 days before entry. Each patient also had to have shown reversibility of $FEV_1 \geq 15\%$ of the initial value following 200–400 µg salbutamol during or within 1 year before the baseline period; diurnal peak expiratory flow (PEF) variation of $\geq 15\%$ for at least 3 days during the last 7 days of the baseline period; or airway hyperresponsiveness to methacholine or histamine ($PC_{20} FEV_1, \leq 8 \text{ mg/mL}$) documented during or within 1 year before the baseline period. All patients received budesonide 1280 µg daily (ex-mouthpiece, equivalent to 1600 µg; Turbohaler™; four inhalations of 160 µg (ex-mouthpiece, equivalent to 200 µg; Turbohaler™) in the morning and four inhalations in the evening) during the pretreatment period. The pretreatment period with high-dose budesonide was included in this study because patients were still inadequately controlled with their current therapy. Response to high-dose budesonide had to be demonstrated; such a response would indicate that ICS dose escalation would improve lung function in the study population. Thus, patients entering the treatment period had to fulfil inclusion criteria and demonstrate improvement in FEV_1 during the pretreatment period of either $\geq 7\%$ or 0.15 L following the increase in their daily ICS dose from 320–640 µg budesonide (or the equivalent) to 1280 µg budesonide. Furthermore, treatment with high-dose budesonide before randomisation helped to establish control of asthma symptoms and lung function, which were then monitored for maintenance in the randomised treatment period.^{16,17}

Patients were randomised (using a computer-generated list at a ratio of 1:1) to ciclesonide 320 µg (ex-actuator, equivalent to 400 µg ex-valve) via a hydrofluoroalkane-MDI without a spacer or budesonide 320 µg (ex-mouthpiece, equivalent to 400 µg; Turbohaler™) once daily in the morning for 12 weeks. Salbutamol (100 µg/puff) served as rescue medication for each patient throughout the study.

Patient assessments

Efficacy

The efficacy of ciclesonide and budesonide once daily was determined by assessments of lung function and control of asthma symptoms. The change in FEV_1 at the end of treatment was the primary endpoint. The FEV_1 , forced vital capacity (FVC), and morning and evening PEF were recorded at each study visit according to American Thoracic Society criteria.¹⁸ Salbutamol was withheld for at least 4 h before each determination. For adults (≥ 18 years of age), predicted values were calculated according to the formula of the European Community for Coal and Steel.¹⁹ For adolescents (12–17 years of age), predicted values were calculated according to previously published values.²⁰ All patients were given a mini-Wright PEF meter and were instructed to read three PEF measurements before rising in the morning and between 6 and 8 p.m. each evening.

The parameters used to assess control of asthma included asthma symptom scores; rescue medication use; number of asthma symptom-free days; rescue medication-free days; and subjective effectiveness rating by investigator and patient assessments, made using the following rating scales: *very effective* (good control of asthma), *effective* (not optimal, but acceptable control of asthma), *slightly effective* (only moderate control of asthma symptoms, improvement desired), and *ineffective* (poor control of asthma). Additionally, asthma scores were recorded on a five-point scale as follows: daytime asthma scores were recorded on a scale from 0 (very well, no symptoms) to 4 (asthma very bad, unable to carry out daily activities as usual); night time asthma scores ranged from 0 (no symptoms, slept through the night) to 4 (bad night, awake most of the night because of asthma). Patients also recorded the number of inhalations per day of salbutamol rescue medication.

The criteria satisfying lack of efficacy included a clinical asthma exacerbation, defined as increasing asthma symptoms and decrease in lung function

requiring treatment with oral steroids (e.g., a decrease in morning PEF on 2 consecutive days by $>30\%$ below the baseline value); a decrease in morning FEV_1 of $\geq 20\%$ of the prestudy value or $<50\%$ predicted; a night time asthma score ≥ 2 on at least four of the seven nights or ≥ 3 on at least two of the seven days; a daytime asthma score of ≥ 3 on at least four of the seven days directly preceding a visit; or another deterioration in lung function that compromised the patient's health.

Safety

All adverse events experienced by a patient or observed by an investigator were recorded at each study visit. All adverse events were classified as mild, moderate, or severe, and were evaluated by investigators for causal relationship to study medication. A physical examination, including vital signs and electrocardiogram, was performed at the start of the baseline period and again at the end of the treatment period. Additional routine laboratory safety parameters included a haematology and full chemistry panel (including hepatic and renal function), urinalysis, and pregnancy test.

Statistical analysis

All patients who received at least one dose of ciclesonide were included in the intent-to-treat (ITT) population, and patients who had no major protocol violations were included in the per-protocol (PP) population. Results obtained from the PP analysis were confirmed by ITT analysis. The primary endpoint was the noninferiority of ciclesonide 320 μg versus budesonide 320 μg administered once daily in the morning based on the difference in FEV_1 from randomisation to the end of treatment. The primary hypothesis for noninferiority was tested using the 95% two-sided confidence interval (95% CI) for differences between treatment groups. Both PP and ITT analyses were performed for noninferiority. Least-squares means and two-sided 95% CI were presented for differences within and between treatment groups. A sample size of 100 patients per treatment group was necessary to ensure a power of 87% to establish a noninferiority of ciclesonide 320 μg versus budesonide 320 μg (noninferiority acceptance limit for the primary efficacy variable FEV_1 was set to -0.200 L). For all endpoints except for the primary efficacy variable FEV_1 , the ITT analysis is reported within text, tables, and figures, unless there are relevant differences in statistical results between the two (ITT and PP) study populations, and PP analysis is reported within the tables.

All secondary variables were analysed in an exploratory manner. Secondary variables FVC and morning and evening PEF from diaries were analysed analogously to FEV_1 (noninferiority acceptance limits were -0.200 L ; and to -25 L/min , respectively). Changes in the sum of asthma symptom scores and number of inhalations of rescue medication between the week before the last visit and the week before randomisation were compared within treatments by Pratt's modification of Wilcoxon signed-rank test and between treatments by Mann-Whitney *U*-tests. Between-treatment comparisons for asthma symptom-free days, rescue medication-free days, and patient-perceived control of asthma symptoms (i.e., no symptoms and no rescue medication use) were analysed by Mann-Whitney *U*-tests. The primary and secondary efficacy endpoints were evaluated by analysis of covariance (ANCOVA).

Results

Patient demographics and baseline disease characteristics

A total of 688 patients were enrolled in the study from 64 centres located in Canada, Hungary, Italy, Poland, Portugal, and Spain, and 359 patients (ITT population) were randomised to treatment (179 to ciclesonide, 180 to budesonide). Of the 359 patients randomised to the two treatments, 320 patients were without protocol violations during the study and represented the PP population. The demographic and baseline disease characteristics were similar between the two treatment groups (Table 1). The majority of the randomised patients (343 out of 359) were Caucasian.

Pulmonary function

During the pretreatment period with budesonide 1280 μg daily, mean FEV_1 levels increased by 0.352 L for the ciclesonide group (from 2.53 to 2.88 L) and 0.319 L for the budesonide group (from 2.42 to 2.74 L). After patients were randomised to either ciclesonide 320 μg or budesonide 320 μg once daily, FEV_1 decreased by 0.18 and 0.23 L, respectively, over 12 weeks of treatment ($P < 0.0001$; PP analysis of within-treatment comparison; Table 2). Ciclesonide was noninferior to budesonide with regard to maintenance of FEV_1 (95% CI = -0.015 , 0.121 for ciclesonide versus budesonide; PP analysis; Table 2). Similar results were obtained by ITT analysis (Fig. 1). There were no significant

Table 1 Demographic and baseline characteristics (*n* = 359).*

Characteristics	CIC 320 µg [†] OD (<i>n</i> = 179)	BUD 320 µg [†] OD (<i>n</i> = 180)
Median age, years (range)	39 (12–72)	42 (12–71)
Sex (male), <i>n</i> (%)	79 (44)	69 (38)
Nonsmokers, <i>n</i> (%)	135 (75)	123 (68)
Smokers/ex-smokers, <i>n</i> (%)	44 (25)	57 (32)
Mean prestudy daily ICS dose, BDP equivalents (µg) [‡]	740	767
Mean FEV ₁ (L ± SD)		
Start of 2-week baseline period	2.60 ± 0.73	2.43 ± 0.59
Start of pretreatment with BUD (1280 µg/day) [†]	2.53 ± 0.70	2.42 ± 0.60
Start of randomised treatment	2.87 ± 0.79	2.74 ± 0.66
Mean FEV ₁ (% predicted ± SD)		
Start of 2-week baseline period	81 ± 8	79 ± 7
Start of pretreatment with BUD (1280 µg/day) [†]	78 ± 8	79 ± 7
Start of randomised treatment	89 ± 9	90 ± 8
Reversibility change in FEV ₁ (% ± SD) [§]	21.1 ± 9.1	23 ± 12.6
Mean morning PEF (diary) (L/min ± SD) [§]	382 ± 104	374 ± 99
Mean PEF variability (% ± SD) [§]	6.7 ± 5.2	6.0 ± 5.0

CIC, ciclesonide; BUD, budesonide; OD, once daily; ICS, inhaled corticosteroid; BDP, beclomethasone dipropionate; FEV₁, forced expiratory volume in 1 s; SD, standard deviation; PEF, peak expiratory flow.

*Intent-to-treat population.

[†]Ciclesonide 320 µg is ex-actuator, equivalent to 400 µg ex-valve; budesonide 320 and 1280 µg are ex-mouthpiece doses, equivalent to 400 and 1600 µg (TurbohalerTM).

[‡]Per-protocol population. Nineteen patients from the ciclesonide group and 20 patients from the budesonide group were found to have major protocol violations. Thus, 160 patients from each treatment group made up the valid cases set for per-protocol population analysis.

[§]Start of randomised treatment.

differences between the two treatment groups with regard to change in FEV₁ at the end of treatment.

While mean FVC levels also decreased in both treatment groups, the decrease in ciclesonide patients (0.12 L; *P* < 0.0001, within-treatment comparison) compared with that in budesonide patients (0.21 L; *P* < 0.0001, within-treatment comparison) was significantly less (95% CI = 0.02, 0.147; *P* = 0.011 for ciclesonide versus budesonide; ITT analysis). Similar results were obtained after PP analysis. For morning PEF, the least-squares mean values over 12 weeks of treatment remained virtually unchanged for the ciclesonide group (−3 L/min; *P* = 0.374), while there was a small but significant decrease in the budesonide group (−10 L/min; *P* = 0.007; ITT analysis) (Table 2; Fig. 2). However, the differences between treatment groups were not statistically significant. Mean evening PEF levels did not significantly change from the beginning of treatment for either ciclesonide or budesonide treatment groups (*P* = 0.50 and 0.179, respectively). PP analysis of morning and evening PEF measures yielded results comparable with the ITT analysis.

Asthma symptom scores and rescue medication use

Although patients were treated with high-dose budesonide (1280 µg daily) during the pretreatment period, there were no significant differences between the two treatment groups in median asthma symptom score sums, night scores, and daytime scores over the treatment period. However, the percentage of asthma symptom-free days was 43.6% in the ciclesonide group compared with 25.8% in the budesonide group (Fig. 3). Additionally, patients treated with ciclesonide experienced a significant reduction in the median rescue medication use over the course of treatment (*P* = 0.009) in contrast to no change in those treated with budesonide (*P* = 0.626), and there was a corresponding significant difference between treatment groups in median rescue medication use (*P* = 0.026; Fig. 4). The median percentage of rescue medication-free days, however, was similar in both groups (57.5% versus 53.6% for ciclesonide and budesonide group, respectively). Similar results were obtained in the PP analysis.

Table 2 Change in lung function at the end of treatment.

Parameter	PP		ITT	
	CIC 320 µg* OD	BUD 320 µg* OD	CIC 320 µg* OD	BUD 320 µg* OD
<i>Spirometry</i>				
FEV ₁ (L)				
Baseline [†]	2.91	2.74	2.86	2.75
Change versus baseline [§]	-0.18	-0.23	-0.17	-0.22
P-value versus baseline	<0.0001	<0.0001	<0.0001	<0.0001
Change versus BUD [§]	0.05		0.05	
95% CI	-0.015, 0.121		-0.007, 0.111	
P-value versus BUD	0.125		0.087	
FVC (L)				
Baseline [†]	3.69	3.4	3.62	3.41
Change versus baseline [§]	-0.12	-0.22	-0.12	-0.21
P-value versus baseline	0.0001	<0.0001	<0.0001	<0.0001
Change versus BUD [§]	0.1		0.08	
95% CI	0.024, 0.172		0.02, 0.147	
P-value versus BUD	0.01		0.011	
<i>Diary</i>				
Morning PEF (L/min)				
Baseline [†]	388	372	382	373
Change versus baseline [§]	-3	-11	-3	-10
P-value versus baseline	0.451	0.007	0.374	0.007
Change versus BUD [§]	8		6	
95% CI	-2, 18		-2, 15	
P-value versus BUD	0.108		0.141	
Evening PEF (L/min)				
Baseline [†]	401	381	394	382
Change versus baseline [§]	-1	-5	-2	-4
P-value versus baseline	0.833	0.16	0.5	0.179
Change versus BUD [§]	4		2	
95% CI	-4, 13		-6, 10	
P-value versus BUD	0.331		0.591	

PP, per-protocol; ITT, intent-to-treat; CIC, ciclesonide; BUD, budesonide; OD, once daily; FEV₁, forced expiratory volume in 1 s; CI, confidence interval; FVC, forced vital capacity; PEF, peak expiratory flow.

*CIC 320 µg is ex-actuator, equivalent to 400 µg ex-valve; BUD 320 µg is ex-mouthpiece, equivalent to 400 µg (Turbohaler™).

[†]Values presented are means, paired values.

[§]Values presented are least-squares means.

A total of 66 patients (18%) withdrew from the study due to lack of efficacy in the ITT population. In the budesonide group, there were more patients (37 (21%)) than in the ciclesonide group (29 (16%)) that withdrew from the study due to lack of efficacy. There were no significant differences between treatment groups with regard to lack of efficacy, physician assessments, or patient self-assessments.

Safety

During the double-blind treatment period, a total of 168 (47%) patients experienced an adverse

event: 52% in the budesonide group and 42% in the ciclesonide group (Table 3). Most adverse events were mild or moderate in intensity and considered "unrelated" or "unlikely related" in all cases. Common adverse events in patients treated with ciclesonide or budesonide included upper respiratory infection (12% and 19%, respectively), asthma (9% and 12%), bronchitis (3% and 3%), pharyngitis (3% and 3%), rhinitis (2% and 3%), voice alteration (2% and 1%), and sore throat (2% and 1%). There were no cases of oral candidiasis in either treatment arm.

Three patients experienced serious adverse events: one patient in the ciclesonide group (exacerbation of asthma), and two patients in the

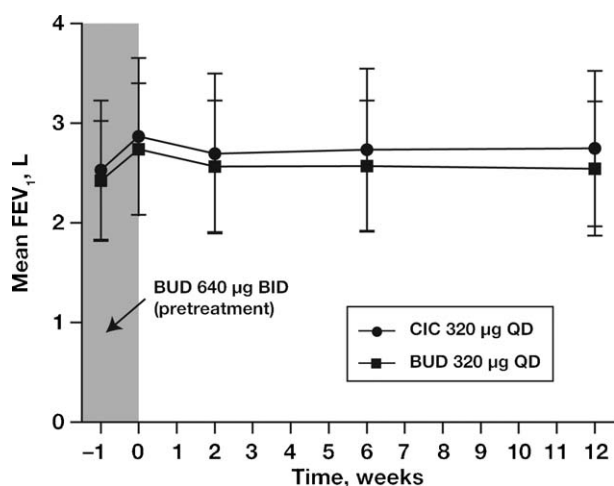


Figure 1 Time course of FEV₁ during 12 weeks of therapy with ciclesonide 320 µg QD and budesonide 320 µg QD. Data are expressed as means \pm SD. FEV₁, forced expiratory volume in 1 s; QD, once daily; CIC, ciclesonide; BUD, budesonide; and BID, twice daily. Ciclesonide 320 µg is an ex-actuator dose, equivalent to 400 µg ex-valve; budesonide 320 µg is an ex-mouthpiece dose, equivalent to 400 µg (TurbohalerTM).

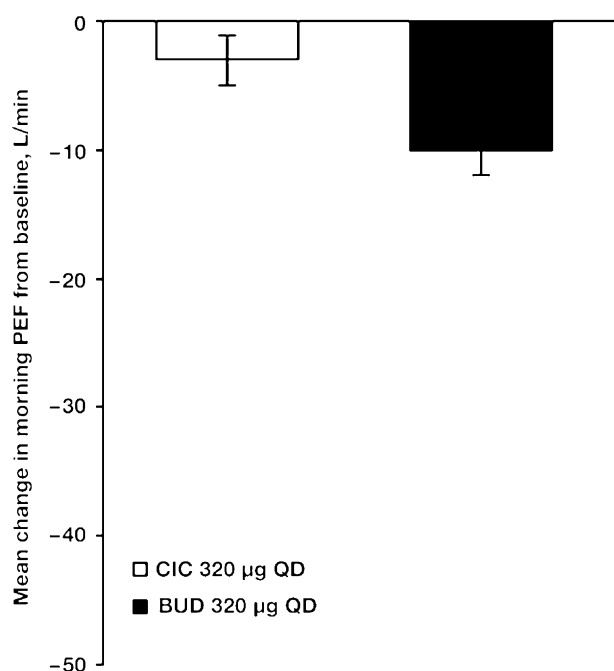


Figure 2 Change from baseline in morning PEF with ciclesonide 320 µg QD and budesonide 320 µg QD. Data represent the intent-to-treat patient population and are based on least-squares means. PEF, peak expiratory flow; QD, once daily; CIC, ciclesonide; BUD, budesonide; and BID, twice daily. Ciclesonide 320 µg is an ex-actuator dose, equivalent to 400 µg ex-valve; budesonide 320 µg is an ex-mouthpiece dose, equivalent to 400 µg (TurbohalerTM).

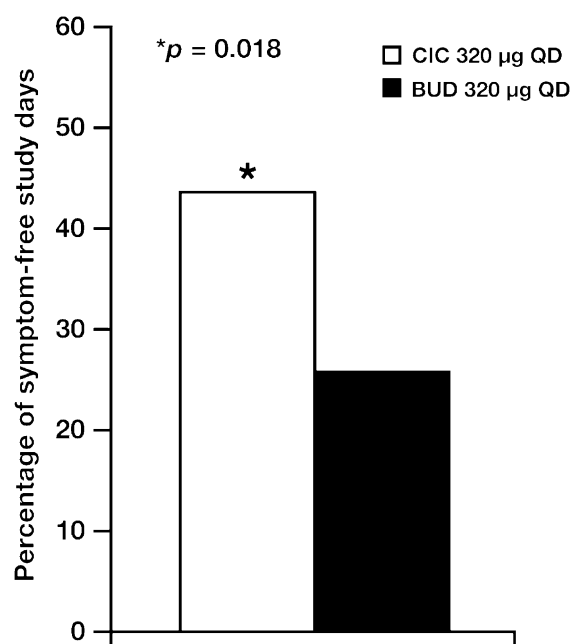


Figure 3 Percentage of patients with symptom-free days based on the intent-to-treat population. Data are presented as medians. CIC, ciclesonide; BUD, budesonide; and QD, once daily. Ciclesonide 320 µg is an ex-actuator dose, equivalent to 400 µg ex-valve; budesonide 320 µg is an ex-mouthpiece dose, equivalent to 400 µg (TurbohalerTM). * $P = 0.018$ versus budesonide.

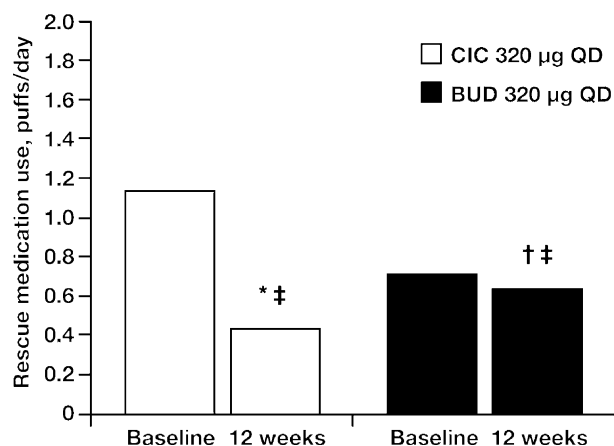


Figure 4 Patients with rescue medication use over 12 weeks of treatment with ciclesonide 320 µg QD and budesonide 320 µg QD. Data represent the intent-to-treat patient population and are presented as medians. CIC, ciclesonide; BUD, budesonide; and QD, once daily. Ciclesonide 320 µg is an ex-actuator dose, equivalent to 400 µg ex-valve; budesonide 320 µg is an ex-mouthpiece dose, equivalent to 400 µg (TurbohalerTM). * $P = 0.009$ versus baseline; † $P = 0.626$ versus baseline; and ‡ $P = 0.026$ versus budesonide.

Table 3 Frequently reported adverse events.

	Patients, <i>n</i> (%)	
	CIC 320 µg* OD (<i>n</i> = 179)	BUD 320 µg* OD (<i>n</i> = 180)
Total adverse events	75 (42)	93 (52)
Upper respiratory infection	22 (12)	34 (19)
Asthma	16 (9)	21 (12)
Bronchitis	6 (3)	6 (3)
Sore throat	3 (2)	2 (1)
Pharyngitis	6 (3)	5 (3)
Sinusitis	3 (2)	3 (2)
Rhinitis	4 (2)	6 (3)
Oral candidiasis	0 (0)	0 (0)
Voice alteration	3 (2)	2 (1)
Flu syndrome	7 (4)	12 (7)

CIC, ciclesonide; BUD, budesonide; OD, once daily.

*Ciclesonide 320 µg is ex-actuator, equivalent to 400 µg ex-valve; budesonide 320 µg is ex-mouthpiece, equivalent to 400 µg (Turbohaler™).

budesonide group (carcinoma of the breast and surgical repair of pre-existing ankle injury). There were no clinically significant laboratory findings or changes in vital signs in either treatment group.

Discussion

The current study demonstrated that ciclesonide 320 µg once daily in the morning was at least as effective as budesonide 320 µg once daily in maintaining lung function and controlling asthma symptoms in patients routinely requiring daily ICS administration. Although differences were small, the fall in FVC at the end of treatment was higher in the budesonide group, and ciclesonide was more effective in maintaining morning PEF. Moreover, ciclesonide showed a significant reduction in rescue medication use compared with budesonide. Furthermore, both treatments showed a good safety profile with low rates of adverse events.

Both ciclesonide and budesonide undergo reversible conjugation with fatty acids in the airway and lung.^{21,22} It is important to note that fatty acid conjugation extends pulmonary retention time and prolongs topical anti-inflammatory activity enabling once-daily treatment regimens.²³ As a consequence, both ciclesonide and budesonide have shown efficacy when administered once daily.^{13,24,25} In the present study, ciclesonide was more effective than budesonide in maintaining lung function and controlling asthma symptoms. This observation may be related to the differences in the physicochemical properties of ciclesonide and

budesonide. Although both corticosteroids form lipid conjugates,^{21,26} lipid conjugates formed by des-CIC are 5-fold more lipophilic than those of budesonide.²⁷ Therefore, the overall retention of the lipid conjugates of des-CIC may be greater than that of budesonide, thereby prolonging anti-inflammatory activity. Moreover, there are differences in the formulation characteristics of budesonide delivered via dry powder inhaler (Turbohaler) and ciclesonide delivered via MDI. Consequently, the lung deposition of ciclesonide inhaled via MDI is ~50% of the delivered dose, which is higher than the deposition that can be achieved by dry powder inhalers.^{28,29}

The study design involved a direct comparison with an active comparator without a placebo arm. Importantly, the target patient population included patients routinely requiring daily administration of moderate doses of ICS to control asthma symptoms. Furthermore, both ciclesonide and budesonide have been shown in earlier clinical trials to be more effective than placebo in improving pulmonary function and control of asthma symptoms in patients with persistent asthma.^{9,30} The pretreatment period of 2–4 weeks with budesonide 1280 µg/day before randomisation was designed to delineate the differences between the two ICS (ciclesonide and budesonide). As expected, following randomisation to ciclesonide or budesonide, FEV₁ decreased in patients treated with both study medications, yet overall, each study drug was comparable in maintaining adequate lung function and control of asthma symptoms over 12 weeks. These results support the findings in a previous study where ciclesonide 80 or 320 µg once daily was

as effective as budesonide 160 µg (ex-mouthpiece, equivalent to 200 µg; Turbohaler™) twice daily in improving lung function and control of asthma symptoms.³¹

In conclusion, a once-daily morning inhalation of ciclesonide 320 µg was at least as effective as budesonide 320 µg in the treatment of persistent asthma. Additionally, ciclesonide was statistically superior to budesonide with regard to FVC, symptom-free days, and rescue medication use. Both agents were safe and well tolerated.

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